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PERSPECTIVE

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Therapeutic drug monitoring of antifungal therapies: do we really need it and what are the best practices?

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ABSTRACT

Introduction: Despite advancements, invasive fungal infections (IFI) still carry high mortality rates, often exceeding 30%. The challenges in diagnosis, coupled with limited effective antifungal options, make managing IFIs complex. Antifungal drugs are essential for IFI management, but their efficacy can be diminished by drug–drug interactions and pharmacokinetic variability. Therapeutic Drug Monitoring (TDM), especially in the context of triazole use, has emerged as a valuable strategy to optimize antifungal therapy.

Areas covered: This review provides current evidence regarding the potential benefits of TDM in IFI management. It discusses how TDM can enhance treatment response, safety, and address altered pharmacokinetics in specific patient populations.

Expert opinion: TDM plays a crucial role in achieving optimal therapeutic outcomes in IFI management, particularly for certain antifungal agents. Preclinical studies consistently show a link between therapeutic drug levels and antifungal efficacy. However, clinical research in mycology faces challenges due to patient heterogeneity and the diversity of fungal infections. TDM's potential advantages in guiding Echinocandin therapy for critically ill patients warrant further investigation. Additionally, for drugs like Posaconazole, assessing whether serum levels or alternative markers like saliva offer the best measure of efficacy is an intriguing question.

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TDM; Therapeutic drug monitoring; invasive fungal infection; echinocandin; posaconazole; isavuconazole; antifungals

1. Introduction

Invasive fungal infections (IFI) have been increasing in incidence over the last decades, presenting a growing healthcare challenge also recognized by the World Health Organization (WHO), which published a list of high priority fungal pathogens including *Aspergillus fumigatus* and the emerging fungal pathogen *Candida auris* in 2022 [1]. Immunocompromised patients, including those with hematological malignancy and hematopoietic stem cell transplantation, undergoing chemotherapy, solid organ transplantation, or living with HIV/AIDS are particularly susceptible to these infections [2–4].

Despite advances both in medical care, and also in the mycological field, IFIs are still associated with high mortality rates often exceeding 30%, in some patient populations reaching nearly 80% [3,5,6]. The challenges associated with the diagnosis, coupled with the limited availability of effective antifungals further exacerbate the complexity of managing IFIs. As the current knowledge of pharmacokinetic properties of antifungal agents matures, the clinical utility subsequently increases. Consequently, many papers were published in recent years, with efforts of pouring new insights into clinical recommendations [7–10].

Pharmacological treatment and prophylaxis with antifungal drugs are essential components in the management and prevention of IFI. However, their efficacy can be hindered through drug interactions, variable pharmacokinetics, and resistance development. To address these challenges, Therapeutic Drug Monitoring (TDM) has emerged as a valuable strategy, especially in the use of triazoles [11,12]. In theory, TDM allows for the optimization of antifungal therapy, tailoring treatment regimens to individual patients' needs while minimizing adverse effects.

Here, we will begin by providing a short overview of the fundamental pharmacokinetic characteristics of the key antifungal agents. Subsequently, we will look at the current guideline recommendations and delve into the evidence regarding the potential benefits of TDM in the context of infection control, adverse events, specific patient population (e.g., renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO)) and potential cost- benefits.

2. Echinocandins

The class of echinocandins (micafungin, caspofungin, anidulafungin, rezafungin) target the cell wall enzyme complex β-1,3-D-glucan synthase, thus interfering with fungal cell wall synthesis [13,14]. They are fungistatic against *Aspergillus spp.* and fungicidal against most *Candida spp.*, including those resistant to fluconazole and have also shown preserved activity against emerging *Candida auris* [15–17]. They are considered the first-line therapy in invasive candidiasis and are also

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Article highlights

- TDM plays a crucial role in achieving optimal therapeutic outcomes.
- Preclinical studies consistently show a link between therapeutic drug levels and antifungal efficacy.
- TDM of echinocandins might be useful in specific patient populations (e.g., obese, critically ill).
- Parameters other than serum concentrations, like saliva levels may aid in the guidance of antifungal therapy.
- Further investigations are required to establish clear cutoff concentrations for clinical utility.

valued for their excellent safety profile and mostly negligible potential for drug–drug interactions [2,18–20].

Echinocandins have a relevant post-antifungal effect and therefore a concentration-dependent activity. Preclinical data suggest C_{max}/MIC (minimal inhibitory concentration) and AUC_{0-24} (area under curve)/MIC as possible markers for optimizing pharmacokinetic/pharmacodynamic (PK/PD) properties of these drugs [10,21]. In animal models, concentration-dependent activity could be demonstrated for all available echinocandins [22–29]. While target AUC/MICs have been suggested by these models, the clinical trials for confirmation of their utilization are lacking [10,29]. Subtherapeutic drug levels were reported in specific patient populations, such as critically-ill [30–35] and obese patients [36,37]. In part, those subtherapeutic levels may be related to insufficient dosing in the approved dosages of the daily echinocandins, a limitation that has been overcome by rezafungin where the recommended dosage provides sufficient levels also in obese patients [38]. In addition to therapeutic failure in patients achieving insufficient drug levels, subtherapeutic levels may be a driver of echinocandin-resistance [21]. Märtson et al. proposed a dose regimen based on body weight (2 mg/kg loading dose with 1.25 mg/kg maintenance dose) to assure adequate drug levels in critically ill patients [39]. Additionally, based on PK simulation the micafungin maintenance dose has to be increased from 100 mg to 200 mg or 300 mg (depending on the MIC of the targeted strain) in patients weighing >125 kg and these patients may also benefit from a loading dose [36]. The mentioned simulation also indicates a possible benefit of an increase of the anidulafungin dose of 25% in patients with >140 kg [37]. While no dose adjustments are recommended for patients with moderate hepatic impairment for micafungin and anidulafungin, caspofungin doses may increase in patients with liver insufficiency. However, this increased exposure did not translate into an increase in adverse events making a dose reduction questionable, especially in critically ill patients [10].

In the cerebrospinal fluid, drug levels are usually very low, outlining no CNS penetration, mostly due to their high molecular weight and excessive protein binding [40]. Furthermore, their penetration into the intraperitoneal fluid is low to moderate with concentrations of about 9–33% in critically ill patients with suspected Candida peritonitis, which poses the risk of treatment failure and development of resistant *Candida* strains [41]. Therefore, TDM of echinocandines may be useful in patient populations which are susceptible to subtherapeutic levels (e.g., critically ill, obese) and in patients with intraperitoneal infections, once more data becomes available to define clear cutoffs and develop management strategies accordingly.

Echinocandin- TDM for the prevention of supratherapeutic effects may be of little utility. They are typically well tolerated with few significant side effects. In studies with much higher doses used than the manufacturer's recommendation, they still showed an excellent safety profile [42–44]. In- vitro, some *Candida spp*. can grow at supratherapeutic echinocandin levels known as a paradoxical 'Eagle' effect. However, the clinical impact of this phenomenon is uncertain and a matter of debate [45].

3. Polyenes

Amphotericin B is the most prominent agent of the polyene-antifungal class. The initial formulation was amphotericin B deoxycholate, which while used for many decades, is no longer endorsed because of dose-limiting side effects, most importantly renal impairment [46]. With the introduction of lipid formulations of amphotericin B, for example, liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC) are now recommended due to their reduced nephrotoxicity [47]. Recently, the poor oral bioavailability may have been overcome by a nano-particle encochleated formulation coating the drug, thus providing more stability, and favorable physico-chemical properties at the surface [48]. Today, mostly L-AmB is used, which is currently the only formulation available in most countries [49]. LAmB primarily distributes to organ sites rich in mononuclear phagocytic cells, with secondary distribution to the kidney, lung, and brain with slow unchanged elimination via the bile and urine [50]. Interestingly, despite its utilization in fungal infections of the central nervous system, low concentrations are detected in the cerebrospinal fluid, with CSF/plasma ratios of < 0.01 for all formulations [51,52]. Additionally, intraperitoneal levels of amphotericin b are variable and lower than serum concentrations with a ratio of about 0.41 in a study with critically ill was seen in patients with Candida peritonitis [53,54].

Amphotericin B displayed a concentration-dependent fungicidal effect in animal models [55–59]. Notably, escalating dose regimes in two randomized controlled trials (RCT) could not demonstrate an additional benefit for the higher dosage group for the treatment of invasive aspergillosis, however, a higher rate of hypokalaemia, and nephrotoxicity in the high-dose group was observed in one [60,61]. The relationship of C_{max} to MIC (C_{max}/MIC) has shown to be the best predictor of efficacy in animal studies, but clinical data to confirm these findings are still lacking [49,50]. A C_{max}/MIC of ≥ 4.5 has been proposed to conduct clinical trials for the evaluation of efficacy, but the range of both animal and human studies is wide (3.8–40.2).

4. Flucytosine

Flucytosine (5-FC), a fluorinated analog of cytosine is one of the oldest antifungal agents, first evaluated as potential antitumor agent [62]. It has no antifungal activity itself, but is

quickly metabolized into 5- fluorouracil (5-FU) in fungal cells [63,64]. After the conversion, 5-FU is incorporated into fungal RNA resulting in an inhibition of protein synthesis [65]. It has a limited spectrum of susceptible fungi including *Candida spp., Cryptococcus spp*. and dematiaceous molds [66,67]. The dose-related efficacy has been demonstrated in animal studies with the maximal number of organisms killed when the MIC of the fungi was exceeded in about 50% of the time-span. However, these observations have never been translated into actual clinical trials [68–70].

Attributable to its low molecular weight and absence of significant protein binding, this compound demonstrates excellent penetration into the CNS, rendering it a valuable combination partner in severe fungal infections affecting the CNS. Based on limited available human data, the CSF/plasma ratio is approximately 0.74 to 0.84 [51]. Furthermore, flucytosine exhibits facile penetration into peritoneal fluid with approximately 65–100% of its serum concentration [53,54].

5-FC has a well-defined profile of side effects, both dose-related and idiosyncratic. It includes bone marrow suppression, gastrointestinal adverse events as well as hepatotoxicity and renal impairment. Dose-dependent toxicities have been shown in clinical trials with the use of higher doses of 5-FC [71–74]. For this reason, TDM in flucytosine usage has been mainly focusing on preventing toxicity with a C_{max} of <100 mg/ml considered to minimize this [11]. To prevent the development of resistance against 5-FC it is mainly used in combination with other antifungals [18,66]. Additionally, a C_{min} <25 mg/ml has shown an increasing mutation rate, resulting in resistance of *C. albicans* and *Nakaseomyces glabratus* (formerly *Candida glabrata*) strains in in- vitro models [75].

As 5-FC is mainly excreted unchanged via urine (about 97%), the risk of accumulation is exceptionally high in patients with renal impairment and a main reason for substantial variability in drug levels [76,77].

5. Triazoles

Triazole antifungals (e.g., voriconazole, posaconazole, fluconazole, isavuconazole, itraconazole) represent a class of pharmacological agents that have gained significant clinical importance due to their potent inhibitory effects on fungal cytochrome P450-dependent enzymes [78]. These compounds are characterized by the presence of a triazole ring in their chemical structure which acts as a potent inhibitor of ergosterol biosynthesis, a vital component of the fungal cell membrane. This disruption of membrane integrity ultimately leads to fungal cell death [79].

The PK/PD- target of triazoles is the relationship between AUC/MIC [80,81]. As in the clinical setting the quantification of the AUC poses practical challenges, C_{min} is determined to estimate an adequate drug concentration over time [82,83].

Triazoles have found widespread clinical utility in the management of various invasive fungal infections, while also representing the backbone of antifungal prophylaxis in patient populations at risk. As they can be administrated both orally and intravenously, they facilitate flexibility in therapeutic regimens, thus positioning them as essential tools in the armamentarium against fungal infections [3,4,19,84]. Due to its restricted indications, itraconazole is not further discussed in this manuscript.

5.1. Voriconazole

Voriconazole shows a complex pharmacokinetic profile, due to its non-linear elimination and therefore considerable interpatient and intrapatient variability [85–89]. The predominant metabolic pathway of voriconazole involves the cytochrome P450 enzyme CYP2C19, rendering it susceptible to fluctuations in drug concentrations as a consequence of allelic polymorphisms of this particular enzyme [90–92]. This metabolism makes it also highly susceptible for drug–drug interactions [93]. While extracorporeal membrane oxygenation seem to lower voriconazole levels, increased levels were seen in patients with morbid obesity (BMI >35 kg/m^2) with doses of 4 mg/kg body weight as well as in critically ill in a hyperinflammatory state [94–100]. In a retrospective analysis of 21 pediatric patients Lempers et al. found that approximately half of the patients required dose adaptation to achieve through concentrations of 1–6 mg/l. Of these, again approximately 50% of the patients needed multiple dose adaptions and one patient was unable to achieve target concentrations outlining the necessity for vigilant monitoring in this patient population with occasionally unpredictable pharmacokinetics [101].

To better predict the metabolism of voriconazole, some authors propose the concomitant measurement of voriconazole-N-oxide, its main metabolite. Wang et al. found an association between CYP2C19 polymorphism and the metabolic rate (C_{min}voriconazole/C_{min}voriconazole-N-oxide), as well as voriconazole through concentrations [102]. A recent prospective study of 61 patients on voriconazole therapy determined a metabolic rate of > 1.15 and < 0.48 as the best predictors of C_{min} <2 mg/l and >5.5 mg/l, respectively. Interestingly, a C-reactive protein value of >96 mg/l was associated with a higher risk for a low metabolic rate [103].

The relationship between the clinical response of voriconazole and serum concentrations have been shown in clinic mostly from retrospective analysis and some prospective evaluations where drug levels of greater than 0.72 mg/l- 2.2 mg/l were associated with fewer treatment failures [89,104–113]. One systematic review and one meta-analysis conducted in this matter concluded that based on the current evidence a cut- off of ≥1 mg/l was the best predictor for treatment response [114,115]. As the penetration into the CNS is well studied in humans with CSF/plasma ratios ranging from 0.22 to 0.88 and even higher levels observed in the brain tissue, voriconazole is the preferred agent in the treatment of CNS aspergillosis, where the European guideline recommends higher thresholds between 2-6 mg/l [51,116]. In a recent prospective study of 19 critically ill patients, voriconazole also showed adequate concentrations in the peritoneal fluid with ratios of the AUC of 0.67 (0.63 to 0.94) compared to plasma, making it a suitable option for intraperitoneal candidiasis [117].

Additionally, voriconazole has an intensive profile of side effects such as neurotoxicity and hepatotoxicity, which have

been associated with supratherapeutic levels [89,104,109–113,118,119]. A threshold on the upper limit to prevent toxicity of voriconazole varies among studies ranging from > 2.13 to 6.7 mg/l [110,112]. However, most non- randomized studies reported increased toxicity at drug levels exceeding 5.0–5.5 mg/l [104,105,113,119]. The meta-analysis concluded that voriconazole levels >6.0 mg/l were the best predictor of toxicity [114].

There are currently two RCTs available, evaluating the clinical utility of TDM in voriconazole use. The RCT conducted by Park et al. published in 2012 found that TDM may reduce drug discontinuation due to adverse events and may improve the response rate in patients with invasive fungal infection [106]. On the other hand, the recently published multicenter RCT from Veringa et al. found no benefit regarding adverse events or treatment response in hematological patients with invasive aspergillosis, also in a subgroup analysis for only probable and proven infections (approximately half of included patients) [120]. This may be due to the fact that in the non-TDM population the initial drug levels of voriconazole were mostly in therapeutic range (80.6%), a much higher rate than observed in prospective studies [121]. This phenomenon could be attributed, in part, to the limited diversity in CYP2C19 observed within this European cohort, which may alter its generalizability to diverse populations.

5.2. Posaconazole

Posaconazole is a triazole derived from itraconazole and available as intravenous formulation as well as oral suspension and delayed release tablet [122]. It serves as the principal therapeutic agent for mold- active prophylaxis and is used in the treatment of invasive mold infections such as invasive aspergillosis and invasive mucomycosis [123–125].

While it is characterized by a substantial protein binding (exceeding 95%), it also exhibits a notable volume of distribution (1800 L) [126]. Posaconazole, particularly the oral suspension, showed high interindividual variability in various populations including healthy individuals, pediatrics, healthy individuals and patients with hematological malignancies [126–134]. In contrast to the oral suspension, inadequate low levels are less common found in those receiving the delayed release tablet or the parenteral formulation [133]. However, in a retrospective analysis of 90 hematological patients on posaconazole, prophylaxis found 24% of the concentrations to be below the mentioned threshold at a standard dose of 1 × 300 mg daily. Diarrhea, male gender and metoclopramide use were independently associated with subtherapeutic levels. After dose adjustment to 2 × 200 mg 89% could reach target attainment at the first steady state measurement [135]. Even with the parenteral formulations highly variable pharmacokinetics in critically ill patients have been reported, which makes TDM an attractive option to assure adequate drug exposure in this susceptible population [9]. In the pediatric patient population highly variable and low trough concentrations were seen with the oral suspension, while in a non-randomized analysis by Döring et al. target concentrations >0.5 mg/l were achieved in approximately 97% of the patients receiving the tablet formulation for antifungal prophylaxis [136,137].

In animal models, an exposure–response relationship could be demonstrated [138–141], however, there is a lack of clinical data which is also complicated by inconsistency, making it difficult to draw a firm conclusion [142–147].

This observation may be partially ascribed to the phenomenon of posaconazole surpassing the serum concentration in the lung tissue, where the primary site of infection is localized. Consequently, C_{min} in the serum might not be an optimal surrogate for accurately representing the AUC related to therapeutic effectiveness [148,149]. Regarding penetration into the CNS the limited data shows inconsistent results into the CSF with CSF/plasma ratios of 0.01–2.25, however, there is currently not enough evidence to recommend posaconazole in fungal CNS infection from a pharmacokinetic point of view [51,122].

For voriconazole saliva concentrations as a non-invasive alternative approach for therapeutic drug monitoring were studied [150]. Whether this approach might be more suitable for TDM for posaconazole has yet to be elucidated.

A lower cutoff of >0.7 mg/l is widely used as it showed an absolute difference in the occurrence of IFIs [151,152]. A meta-analysis from 2018 identified 28 studies in this matter and found a higher incidence of breakthrough infections in patients at trough concentrations of <0.5 mg/l, while no additional benefit could be observed at concentrations of ≥0.7 mg/l compared to a cutoff value of 0.5 mg/l [153].

Regarding the lower threshold in therapy of invasive fungal infections, an average serum concentration of 1.25 mg/l showed better treatment responses in patients with salvage treatment for invasive aspergillosis [154]. Most guidelines recommend a target C_{min} of >1 mg/l [3,116]. However, Dekkers et al. proposed a higher target of 1.8 mg/l in the empiric treatment of invasive fungal infection to cover all sensitive strains, when targeting AUC/MIC- values greater than 200 [155].

Posaconazole is a relatively well tolerated and safe antifungal agent, with a side effect profile including hepatotoxicity, hypokaliaemia, pseudohyperaldosteronism and QT prolongation [156–160].

Again, the data showing the relationship between posaconazole trough levels and adverse events are conflicting. It is mostly derived from retrospective analysis, with some studies suggesting associations with toxicity as low as C_{min} >1.835 mg/l, with higher rates observed at higher posaconazole serum levels versus no observed correlation between trough concentrations and adverse events [146,161–165]. In a retrospective analysis of patients with posaconazole therapy Nguyen et al. found an association between higher posaconazole levels (3 mg/l vs 1.2 mg/l) and pseudohyperaldosteronism [161].

5.3. Isavuconazole

In 2015, isavuconazole (ISA) was introduced as a new addition to the azole family. Its efficacy and favorable side effect profile has led to its rapid and frequent utilization in managing fungal infections, with dosing experience accumulated over time [19,116,166]. Plasma target concentration of 1 mg/l was defined as the EUCAST antifungal clinical breakpoint for *Aspergillus fumigatus* and is clinically recommended as target

[167]. While threshold concentration of 2 mg/l is also proposed, results greater than 4.87 mg/l were associated with increased adverse events [168,169].

One ISA advantage is a linear dose–concentration relationship (PK/PD Index 24-hr AUC/MIC [169,170]. However, in critically ill patients, ISA showed high variability, with a median observed minimum concentration below 2 mg/L, especially in patients with a BMI ≥ 25 and septic patients [171,172]. Although some evidence suggests that ISA is not readily eliminated through dialysis [173], a study involving 22 critically-ill patients showed a 42% reduction in ISA concentration post dialysis [174]. Recently, Jansen et al. proposed that previous findings from pharmacokinetic and pharmacodynamic research on isavuconazole, which assume a constant protein binding, should be reconsidered to investigate such variabilities [175]. In ECMO patients, a stepwise approach aided by real-life TDM has shown that a 400 mg loading dose of isavuconazole is suitable to achieve rapid median plasma concentrations of ≥1 mg/L without reaching a toxic range [176,177]. For individuals with severe hepatic impairment (Child-Pugh Class C), a 50% dosage reduction based on pharmacokinetic data is suggested [178]. A recent case report of aspergillosis in primary biliary cirrhosis (Child-Pugh class B) setting underlined the value of TDM, managing initial concentrations of 17.8 mg/L to a successful treatment over 35 weeks [179]. Regarding the management of CNS infection pharmacokinetic data are scarce. Pharmacokinetic studies in rats showed a brain/plasma concentration ratio of about 1, which could be replicated in a case report in a patient with cerebral abscess due to aspergillosis (brain/plasma ratio approximately 0.9). A retrospective analysis of patients of the VITAL or SECURE trials further supports its clinical usage in fungal infections of the CNS [180,181]. In peritoneal fluid, concentrations derived from 16 critically ill neutropenic patients were highly variable ranging from 13% to 63% (mean 36%) of the related plasma concentration [182].

Isavuconazole is available in bioequivalent oral and intravenous formulations, with a bioavailability of 98% [183]. While caution should be taken when administering via enteral feeding tube, as lower doses may be available, TDM could be shown to be a safe option in these patients, primarily children [184,185]. Average serum half-life of isavuconazole (130 hours) is twice as long as that of posaconazole (20–66 hours), which may be relevant in the outpatient setting/for prolonged oral treatment duration demonstrated a linear increase of 0.032 mg/L per day of treatment in intrapatient variability [168,169]. Available data suggest that isavuconazole shows fewer inter- and intraindividual variability compared to other azoles. Nevertheless, TDM can minimize uncertainty of reaching adequate levels and may reduce adverse events in preventing unnecessary high levels [186,187].

5.4. Fluconazole

Fluconazole is a valuable option when treating yeast infections like *Candida* and *Cryptococcus spp*., but the number of fluconazole-resistant species are increasing [188,189]. Unlike other azole-antifungals, it shows a high solubility in water. About 12% is protein bound, has a volume distribution of about 0.75 l/kg and is mainly excreted via the kidney, therefore requiring a dose adaption in the case of renal impairment [190–192]. Fluconazole is well absorbed with an oral bioavailability of about 90%, which appears to not be altered by food intake, gastric pH, or gastrointestinal surgery [190,193,194]. However, a substantial inter- and intraindividual variability has been observed in recent studies in critically ill and obese males [195–198]. CSF concentrations reach approximately 60–86% of the related plasma concentrations and it also has a good penetration into the peritoneal fluid (about 85%) making it a suitable option for infections with susceptible fungi at mentioned sites [51,54,199].

Fluconazole has displayed a steep dose-response curve in the murine model [200,201]. Based on Monte-Carlo simulation, the European Committee on Antimicrobial Susceptibility Testing recommends a AUC/MIC of > 100, which should be ensured with C_{min} values of about 10-15 mg/l for *Candida* strains with MIC ≤2 mg/l [199,202–204]. Indeed, Pai et al. found a cutoff of C_{min} of 12 mg/l being associated with beneficial outcomes in non-neutropenic patients with candidemia, although this difference was not statistically significant [202]. Righi et al. found that C_{min} values >11 mg/l significantly correlated with clinical success in liver transplant recipients with candidiasis [205].

Fluconazole represents a good safety profile with side effects including hepatotoxicity, rash and QT prolongation, but these have not yet been put into context of fluconazole serum levels [206–208].

6. Conclusion

In conclusion, the utility of TDM in managing IFIs is evident, particularly for certain antifungal agents. TDM offers the potential to enhance treatment efficacy, reduce adverse events and has shown to reduce resistance, ultimately improving patient outcomes. As the understanding of antifungal pharmacokinetics and pharmacodynamics continuously evolves, incorporating TDM into clinical practice is essential. TDM can be a valuable tool in the treatment and prevention of IFIs, contributing to more effective, safe, and personalized treatment. However, continued endeavors are required to gain a more profound understanding of the relationship between drug exposure, toxicity, and therapeutic response, particularly concerning specific antifungal agents like tablet and parenteral formulations of posaconazole, with the objective of establishing precise thresholds for clinical application.

7. Expert opinion

Antifungal agents present various attributes that make them appealing candidates for the implementation of TDM, albeit for diverse reasons. TDM serves a dual purpose by mitigating severe side effects, such as those associated with elevated flucytosine levels, as well as by striving to attain therapeutically effective levels, e.g., in the case of voriconazole. The potential of TDM has been demonstrated, especially in critically ill patients, owing to the substantial variability in drug concentrations. This patient population, with their additional physical constraints and altered organ function, may benefit significantly from optimized dosage management. Preclinical investigations have consistently demonstrated a discernible correlation between therapeutic drug levels and antifungal efficacy across all the aforementioned

antifungal substances. Although it is noteworthy that this correlation does not consistently manifest in clinical studies, since it emanates from controlled laboratory conditions and could be reproduced it is reasonably assumed to be indicative of an underlying pharmacodynamic relationship.

Nonetheless, clinical research in mycology encounters several practical challenges. First and foremost, patient populations exhibit considerable heterogeneity, rendering the comparison of distinct groups, such as organ transplant recipients, hematological patients, and critically ill individuals (with further substantial variations within these categories) inherently challenging. Additionally, the spectrum of underlying infections is highly diverse and contingent on numerous factors, further complicating direct comparisons. Moreover, the relatively low incidence of fungal infections has resulted in a paucity of randomized controlled studies that could effectively mitigate these inherent differences. Furthermore, regarding the broadspectrum triazole antifungals (voriconazole, posaconazole, isavuconazole), these are primarily employed in the prophylaxis and treatment of mold infections where precise diagnosis and pathogen identification are often unattainable. Consequently, this scenario introduces a notable risk of bias when assessing the clinical pharmacodynamics of antifungal agents.

Despite the blurred perspective, an increasingly clear picture emerges from the number of smaller studies, which leads to the narrowing of optimal therapeutic levels. For instance, the optimal dosing of voriconazole appears to fall within the range of steady state trough levels at 2–4 mg/l, with recommended therapeutic trough levels spanning from 1 to 6 mg/l.

As the contours of this landscape sharpen, it is plausible that clinicians will be more readily persuaded regarding the efficacy of TDM, thus fostering its wider adoption in practical clinical settings. Current TDM recommendations based on the provided data are presented in Table 1.

Table 1. Recommendations for TDM based on the evidence provided (PK/PD target: Pharmacokinetic/Pharmacodynamic Target; RRT: renal replacement therapy, ECMO: extracorporeal membrane oxygenation, LTX: liver transplant).

Antifungal	TDM	Indications	Timing on first sample	PK/PD Target	Timing of re-sampling	Target serum concentrations	Comment
Echinocandines	may be useful	-	-	$AUC_{0\text{-}24\ h}$/MIC	-	-	Potential benefit in the critically ill, those with obesity and pediatric patients to ensure adequate exposure
LAmB	Insufficient data	-	-	C_{max}/MIC	-	-	-
Flucytosine	All patients	Prevent toxicity, Prevent resistance	3 days after first dose	AUC/MIC	Once weekly	C_{max} <100 mg/l C_{min} >25 mg/l	-
Voriconazole	All patients	Prevent toxicity Ensure therapeutic levels	48 hours after first dose (loading dose) After 5 days (no loading dose)	$AUC_{0\text{-}24\ h}$/MIC	Changes in Interacting medication Concerns about absorption Suspicion of breakthrough infection Suspicion of toxicity 5–7 days after dose adjustment	C_{min} 1–5.5 mg/l	Potential additional benefit of a narrower range (2-4 mg/l) especially in case of hepatic impairment, empiric therapy, unknown MIC
Posaconazole	All patients with oral solution All patients with treatment	Ensure adequate levels	7 days after first dose	$AUC_{0\text{-}24\ h}$/MIC	Changes in Interacting medication Concerns about absorption Suspicion of breakthrough infection Suspicion of toxicity 7 days after dose adjustment	C_{min} >0.7 mg/l for prophylaxis C_{min} >1 mg/l for treatment	C_{min}>;(2)-4 mg/l might be associated with increased toxicity
Isavuconazole	Critically ill, obesity, RRT, ECMO, hepatic impairment	Ensure adequate levels	3 days (critically ill/ ECMO) 5 days after first dose	$AUC_{0\text{-}24\ h}$/MIC	Changes in Interacting medication Concerns about absorption Suspicion of breakthrough infection Suspicion of toxicity 5–7 days after dose adjustment	C_{min} >1 mg/l	C_{min} >5 mg/l might be associated with increased toxicity Follow-up measurements in prolonged treatment i.e. monthly (linear C_{min} increase of 0.032 mg/L per treatment day)
Fluconazole	Critically ill, LTX, RRT, renal impairment, pediatrics	Prevent accumulation Ensure adequate levels	5 days after first dose	$AUC_{0\text{-}24\ h}$/MIC	Changes in Interacting medication Concerns about absorption Suspicion of toxicity	C_{min} >12 mg/L	A dose reduction might be applied in the case of C_{min} >20-25 mg/l. This is not expected to increase efficacy while increasing the potential for drug-drug interactions and toxicity

While significant progress has been made, there is still much to achieve. Further investigations are required to assess the potential advantages of a TDM-guided approach to echinocandin therapy in critically ill patients and potentially uncover practical thresholds. In the case of posaconazole, the question arises whether serum levels represent the optimal surrogate marker for assessing efficacy, both in prophylactic and therapeutic contexts. An alternative trough level measured in saliva offers the advantage of noninvasive assessment, providing a localized measure near the site of infection.

In summary, new evidence emerges for the potential utility for TDM, in different settings also for antifungal drugs without clear recommendation. However, further research is needed to elucidate the circumstances where TDM might be beneficial, as well as to define an optimal target range for clinical practice.

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